REMARKS

Claims 1 to 34 were pending in the application. Claims 6, 7, and 22-28 were withdrawn as being drawn to non-elected inventions. Claims 1-5, 8-21, and 29-34 were under active consideration.

Claim 1 has been amended to recite that the multiple dose schedule comprises a first course of administration comprising multiple doses, followed by a second course of administration, as described, for example, on page 35, lines 20-23 and in previous claims 31-34. Claims 31, 32 and 34 have been canceled, without prejudice or disclaimer.

Claim 1 and withdrawn claims 22 and 26 have also been amended to delete the phrase "modified forms thereof."

In addition, claims 2-4 have been amended accordingly to refer to one or more mucosal administrations. Claim 15 has been amended to recite that the term "elements" refers to sequences, as described for example on page 15, line 30 to page 16, line 1, of the specification. Claims 5, 19-21 and 33 have also been amended as shown above.

Thus, claims 1 to 30 and 33 are pending as shown above and claims 1-5, 8-21, 29, 30 and 33 are under active consideration.

Amendment of the claims is made without prejudice, without intent to abandon any originally claimed subject matter, and without intent to acquiesce in any rejection of record. Applicants expressly reserve the right to file one or more continuing applications directed to the subject matter of the canceled or withdrawn claims.

35 U.S.C. § 112, 2nd Paragraph

Claims 15 and 30 have been rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for reciting "elements" from two or more alphaviruses. (Office Action, pages 2-3).

Claim 15 has been amended to recite that the alphavirus vector comprises sequences from two or more alphaviruses. Support for this amendment is found in the specification, for example, at page 15, line 30 to page 16, line 1.

In view of the foregoing amendments, Applicants respectfully request that the rejection of claims 15 and 30 under 35 U.S.C. § 112, second paragraph be withdrawn.

35 U.S.C. § 112, 1st Paragraph

Claims 1-5, 8-21, and 29-34 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly not enabled or described by the specification as-filed. (Office Action, pages 3-5). In particular, it is alleged that modified forms of the antigens are not enabled or described in the specification. *Id.* Harcourt et al. (1998) is cited in support of the enablement rejection. *Id.*

In an effort to advance prosecution, and without acquiescing to the present rejections, claim 1 has been amended to delete the phrase "or modified form thereof".

Applicants submit the as-filed specification clearly enables and describes the use of modified forms of any antigen, see for example on page 11, lines 10-14 and Section B on page 23, line 19 to page 27, line 23, including ample disclosure regarding modified forms of HIV antigens on pages 24-27. The specification discloses that an antigen includes proteins with modifications, such as deletions, additions and substitutions to the native sequence, so long as the protein maintains the ability to elicit an immune response. In addition, Harcourt does not change the fact that it was well known as of Applicants' filing date that any antigenic polypeptide could tolerate many modifications and still retain its ability to elicit an immune response. See, for example, U.S. Patent No. 5,792,459; WO 00/39302; and WO 00/39304, which are cited in the present specification at pages 25-27.

Reconsideration and withdrawal of the enablement and written description rejections are respectfully requested.

35 U.S.C. § 102

A. Malone

Claims 1-5, 8-14, 16-21, and 29-34 have been rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by U.S. Patent No. 6,110,898 (hereinafter "Malone"). It is alleged that Malone discloses a method of inducing a mucosal immune response wherein an antigenic polynucleotide is administered to the vaginal, nasal or rectal mucosal membranes of a subject according to a multiple dose schedule (Office Action, page 6, citing abstract, lines 2-4; col. 14, lines 64-66; col. 15, lines 57-62; and col. 17, lines 14-17 and 61-63 of Malone).

The Office Action also alleges that Malone inherently discloses both presenting an antigenic polynucleotide to dendritic cells and eliciting an HLA class I or HLA class II response. *Id.*

Finally, in response to Applicants previous remarks, it is alleged that the claims do not require a cellular and humoral immune response. (Office Action, page 9).

Applicants traverse the rejection and supporting remarks.

The claims under examination are directed to methods of eliciting an immune response in a subject by mucosally administering a gene delivery vehicle in a multiple dose schedule. Furthermore, the multiple dose schedule includes a primary course of administration comprising a multiple dosing schedule, followed by a second course of administration. Therefore, contrary to the Examiner's assertion on page 8 of the Office Action, the specification clearly discloses both a multiple dose scheduling involving single prime/single boost schedules as well as the particular multiple dosing schedules as claimed.

Malone does not describe or demonstrate multiple dose schedules, as claimed. Instead, the only mention in Malone of anything other than a single dose is at col. 17, lines 14 to 22, where priming and boosting are mentioned generally. Not only is there nothing in this passage of Malone about multiple dose schedules as claimed, the reference arguably teaches away from the claimed methods by stating that the priming dose (*e.g.*, corresponding to the multiple dosing first course in Applicants' claims) is a single dose. *See,* col. 17, lines 21-22 of Malone stating that "...the priming dose of antigen-encoding polynucleotide may be followed by booster and/or maintenance doses of antigen." Thus, Malone does not teach a multiple dose schedule as claimed and, accordingly, cannot anticipate any of the pending claims.

Applicants further traverse the assertion that Malone "inherently" discloses presenting an antigenic polynucleotide to dendritic cells and/or eliciting an HLA class I and HLA class II response. In order to inherently anticipate a claim, the Office must provide factual and technical grounds establishing that the inherent feature necessarily flows from the teachings of the reference. *See, e.g., Ex parte Levy*, 17 USPQ2d 1461, 1464 (BPAI 1990). Inherency cannot be established by probabilities or possibilities. *See, e.g., Continental Ca Co. USA, Inc. v. Monsanto Co.* 20 USPQ2d 1746, 1749 (Fed. Cir. 1987).

The Office has not shown that Malone inherently discloses antigen presentation by dendritic cells. In particular, dendritic cells are not the only antigen presenting cells in mucosal tissues. B-cells and macrophages also act as antigen presenting cells. Accordingly, Malone's demonstration that IgA and IgG responses to β-gal were observed does not necessarily mean that the β-gal was presented by dendritic cells. Similarly, Malone is silent as to HLA class I or class

II responses. Thus, the Office has not its burden of showing that any of the claimed features are inherently disclosed in Malone.

Finally, with regard to the statement on page 9 of the Office Action regarding the immune response generated, Applicants agree that the claims as pending generally require an immune response. The previous remarks showing that Malone fails to teach or suggest any sort of cellular immune response were directed to previously pending claims in which the response was a cellular response alone. As correctly noted by the Examiner, the claims now encompass any immune response.

For the reasons set forth above and in view of the foregoing amendments, Applicants respectfully submit that the rejection based on Malone may be withdrawn.

B. Belyakov

Claims 1, 3, 5, 8-20, and 31-34 have been rejected under 35 U.S.C. § 102 as allegedly being anticipated by Belyakov et al. (J. Virol. (1998) 72:8264-8272), hereinafter "Belyakov." In particular, the Office Action alleges that Belyakov et al. disclose intrarectally administering a modified vaccinia virus Ankara that encodes an HIV-1 antigen and administering the virus multiple times (Office Action, page 7).

As noted above, the pending claims are directed to methods involving a primary course of administration comprising multiple dosings, followed by a second course of administration. By contrast, Belyakov describes, at best, a single dose for priming and a single dose for boosting (Belyakov, p. 8265, 1st column, 4th full paragraph, emphasis added):

> We used either **a single dose** of virus for immunization (intraperitoneal [i.p.] or i.r.) or one **single** dose plus **one** boosting dose (of 1×10^7 or 1×10^8 PFU) for i.r. immunization.

Thus, Belyakov does not describe or demonstrate a multiple dosing schedule comprising a first multiple dosing course and a second multiple dosing course, as claimed. As such, withdrawal of this rejection is respectfully requested.

C. Kano

Claims 1, 2, 5, 8, 11, 12, 18-20, and 31-33 have also been rejected under 35 U.S.C. § 102 as allegedly being anticipated by Kano et al. ("Induction of SIV-Specific Cellular Immune Responses by Using Recombinant Sendai Viral Vector" (2000) 7th Conf. Retrov. and Opportun. Inf.), hereinafter "Kano." Kano is alleged to disclose multiple intranasal administrations of a recombinant Sendai vector. (Office Action, page 7).

Applicants respectfully traverse the rejections under 35 U.S.C. § 102 on the following grounds.

Like Malone and Belyakov, Kano fails to disclose a method of generating an immune response by a first course of administration comprising multiple dosings followed by a second course of administration. Instead, Kano teaches 3 inoculations (on weeks 0, 4 and 14). *See,* 3rd paragraph of Kano.

Since Kano does not describe or demonstrate a multiple dosing schedule as claimed, withdrawal of this rejection is respectfully requested.

35 U.S.C. § 103

Claim 15 has been rejected under 35 U.S.C. § 103(a) as being unpatentable over the reference of Malone et al. (U.S. Patent No. 6,110,898). It is alleged that it would have been obvious to modify Malone's SFV vector to include elements from other alphaviruses.

Applicants respectfully traverse the rejection and supporting remarks.

To support an obviousness rejection under 35 U.S.C. § 103, "all the claim limitations must be taught or suggested by the prior art." M.P.E.P. § 2143.03. In addition, "the teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on Applicant's disclosure." M.P.E.P. § 706.02.

Pending claim 15 is drawn to a method of mucosal immunization according to a multiple dose schedule and in which the antigen is delivered using an alphavirus vector comprising sequences from two or more alphaviruses.

For the reasons above, Malone does not teach or suggest multiple dosing schedules as claimed. Nor does Malone teach or suggest alphavirus vectors including sequences from two or more alphaviruses. Indeed, Malone uses vectors including sequences only from SFV. *See,* col. 17, lines 30-33 of Example 1 of Malone. The Office has not provided any reason or evidence as to why one of ordinary skill would have been motivated to modify Malone to arrive at

Applicants' claimed invention.

Therefore, Malone does not teach or suggest the methods of claim 15 and withdrawal of the rejection under 35 U.S.C. § 103(a) is respectfully requested.

CONCLUSION

In light of the above remarks, Applicants submit that the present application is fully in condition for allowance. Early notice to that effect is earnestly solicited.

The Commissioner is hereby authorized to charge any fees and credit any overpayment of fees which may be required under 37 C.F.R. §1.16, §1.17, or §1.21, to Deposit Account No. 18-1648.

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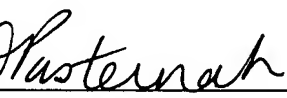
By: 
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